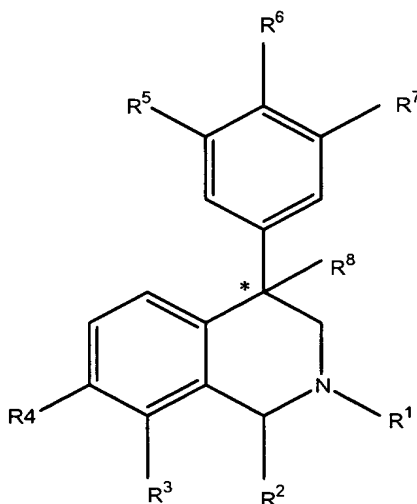


CLAIMS:

What is claimed is:

1. A method of treating chronic or neuropathic pain, treating or preventing
 5 migraine headaches, or treating stress, urge or mixed urinary incontinence comprising
 administering to a patient in need thereof an effective amount of a compound of the
 formula (1):



(1)

wherein:

the carbon atom designated * is in the R or S configuration;

R¹ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl or C₄-C₇
 cycloalkylalkyl, each of which is optionally substituted with from 1 to 3 substituents
 15 independently selected at each occurrence thereof from C₁-C₃ alkyl, halogen, Ar, -CN,
 -OR⁹ and -NR⁹R¹⁰;

R² is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇
 cycloalkylalkyl or C₁-C₆ haloalkyl;

R³ is H, halogen, -OR¹¹, -S(O)_nR¹², -CN, -C(O)R¹², -C(O)NR¹¹R¹², C₁-C₆ alkyl,
 20 C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl or C₄-C₇ cycloalkylalkyl and wherein
 each of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₄-C₇ is
 optionally substituted with from 1 to 3 substituents independently selected at each
 occurrence thereof from C₁-C₃ alkyl, halogen, -CN, -OR⁹, -NR⁹R¹⁰ and phenyl which is
 optionally substituted 1-3 times with halogen, cyano, C₁-C₄ alkyl, C₁-C₄ haloalkyl, or
 25 C₁-C₄ alkoxy, -CN, -OR⁹, or -NR⁹R¹⁰;

R^4 is aryl selected from phenyl, naphthyl and indenyl, or heteroaryl selected from pyridyl, pyrimidinyl, triazinyl, triazolyl, furanyl, pyranyl, indazolyl, benzimidazolyl, quinolinyl, quinazolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, benzthiazolyl, purinyl, isothiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, oxadiazolyl and thiadiazolyl, wherein the aryl or heteroaryl group is optionally substituted with from 1 to 4 R^{14} substituents;

R^5 and R^6 and R^7 are each independently H or are selected from halogen, $-OR^{11}$, $-NR^{11}R^{12}$, $-NR^{11}C(O)R^{12}$, $-NR^{11}C(O)_2R^{12}$, $-NR^{11}C(O)NR^{12}R^{13}$, $-S(O)_nR^{12}$, $-CN$, $-C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl, and wherein each of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and C_4-C_7 cycloalkylalkyl is optionally substituted with from 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, $-CN$, $-OR^9$, $-NR^9R^{10}$ and phenyl which is optionally substituted 1-3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy, $-CN$, $-OR^9$, or $-NR^9R^{10}$; or R^5 and R^6 may be $-O-C(R^{12})_2-O-$;

R^8 is H, halogen or OR^{11} ;

R^9 and R^{10} are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, $-C(O)R^{13}$, phenyl or benzyl, where phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy;

or R^9 and R^{10} are taken together with the nitrogen to which they are attached to form a piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine ring;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, $-C(O)R^{13}$, phenyl or benzyl, where phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^{12} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, phenyl or benzyl, where phenyl or benzyl is optionally substituted 1 to 3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

or R¹¹ and R¹² are taken together with the nitrogen to which they are attached to form a piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine ring, with the proviso that only one of R⁹ and R¹⁰ or R¹¹ and R¹² are taken together with the nitrogen to which they are attached to form a piperidine,

5 pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine ring;

R¹³ is C₁-C₄ alkyl, C₁-C₄ haloalkyl or phenyl;

n is 0, 1, or 2; and,

R¹⁴ is independently selected at each occurrence from a substituent selected from the group: halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -NR¹¹C(O)R¹², -NR¹¹C(O)₂R¹², -NR¹¹C(O)NR¹²R¹³, -S(O)_nR¹², -CN, -C(O)R¹², -C(O)NR¹¹R¹², C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, and C₄-C₇ cycloalkylalkyl where C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₄-C₇ cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from the group consisting of C₁-C₃ alkyl, halogen, Ar, -CN, -OR⁹, and -NR⁹R¹⁰, or
 15 an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or prodrug thereof.

2. A method of claim 1, wherein R¹ is C₁-C₆ alkyl.

20 3. A method of claim 2, wherein R¹ is methyl.

4. A method of claim 1, wherein R² is H, C₁-C₆ alkyl or C₁-C₆ haloalkyl.

5. The compound of claim 4, wherein R² is H or C₁-C₆ alkyl.

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6. A method of claim 5, wherein R² is H.

7. A method of claim 1, wherein R³ is H, halogen, -OR¹¹, -S(O)₂R¹², C₁-C₆ alkyl or substituted C₁-C₆ alkyl.

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8. A method of claim 7, wherein R³ is H.

9. A method of claim 1, wherein R⁴ is phenyl optionally and independently substituted from 1 to 4 times with R¹⁴.
10. A method of claim 9, wherein the R⁴ is phenyl, 2-chlorophenyl, 3-chlorophenyl, 4 chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl or 4 dimethylaminophenyl.
11. A method of claim 1, wherein R⁴ is pyridyl, pynmidinyl, triazinyl, triazolyl, furanyl, pyranyl, indazolyl, benzimidazolyl, quinolinyl, quinazolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, benzthiazolyl, puninyl, isothiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, oxadiazolyl, or thiadiazolyl, which is optionally substituted 1-4 times with R¹⁴.
12. A method of claim 11, wherein R⁴ is 4-methyl-2-furanyl, 5-methyl- 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 3,5-dimethyl-4-isoxazolyl, 2- pyridyl, 3-pyridyl, 4-pyridyl, 2-methoxy-3-pyridyl, 6-methoxy-3pyridyl, 3, 5-pyrimidinyl or 2,6-pyrimidinyl.
13. The compound of claim 1, wherein R⁵, R⁶ and R⁷ are each independently selected from the group: H, halogen, -OR¹¹, -NR¹¹R¹², -, -S(O)₂R¹², -C(O)R¹², and optionally substituted C₁-C₆ alkyl.
14. A method of claim 13, wherein R⁷ is H.
15. A method of claim 14, wherein of R⁵ and R⁶ are each H, F, Cl, OH, OCH₃ or CH₃- .
16. A method of claim 1, wherein R⁸ is H, OH, or F.
17. A method of claim 1, wherein
R¹ is C₁-C₆ alkyl;
R² is H, C₁-C₆ alkyl or C₁-C₆ haloalkyl;
R³ is H, halogen, -OR¹¹, -S(O)₂R¹², C₁-C₆ alkyl or substituted C₁-C₆ alkyl;
R⁴ is aryl or heteroaryl; and

R^5 , R^6 and R^7 are each independently selected from the group: H, halogen, -OR¹¹, NR¹¹R¹², -S(O)₂R¹², -C(O)R¹², C₁-C₆ alkyl and substituted C₁-C₆ alkyl.

18. A method of claim 1, wherein R^1 is methyl;

5 R^2 is H;

R^3 is H;

R^5 and R^6 are each independently selected from the group: H, F, Cl, OH, OCH₃, and CH₃;

R^7 is H or F;

10 R^8 is H, OH, or F; and

R^4 is phenyl, pyridyl, pyrimidinyl, triazinyl, triazolyl, furanyl, pyranal, indazolyl, thienyl, imidazolyl, thiazolyl, purinyl, isothiazolyl, indolyl, pyrrolyl, oxazolyl, isoxazolyl, or pyrazolyl, each of which R^4 is optionally and independently substituted from 1-4 times with R^{14} .

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19. A method of claim 1, wherein R^1 is methyl;

R^2 is H;

R^3 is H;

R^5 and R^6 are each H, F or CH₃;

20 R^7 is H;

R^8 is H; and

R^4 is phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3 methoxyphenyl, 4-methoxyphenyl, 4-dimethylaminophenyl, 4-methyl-2-furanyl, 5 methyl-2-furanyl and 3-furanyl, 2-thienyl and 3-thienyl, 3,5-dimethyl-4- isoxazolyl, 2 pyridyl, 3-pyridyl, 4-pyridyl, 2-methoxy-3-pyridyl and 6-methoxy-3-pyridyl 3,5 pyrimidinyl or 2,6-pyrimidinyl.

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20. A method according to claim 1, wherein the carbon atom designated * is in the R configuration.

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21. A method according to claim 1, wherein the carbon atom designated * is in the S configuration.

22. A method comprising a mixture of stereoisomerisms compounds of claim 1 wherein the carbon atom designated * is in the S or R configuration.
23. A method according to claim 1, selected from the group:
- 5 4,7-diphenyl-2-methyl- 1,2,3,4-tetrahydroisoquinoline;
 7-(2-chloro)phenyl-2-methyl-4-phenyl- 1,2,3,4-tetrahydroisoquinoline;
 7-(3-chloro)phenyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 7-(4-chloro)phenyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 7-(2-methoxy)phenyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 10 7-(3-methoxy)phenyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 7-(4-methoxy)phenyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 7-(4-N,N-dimethylamino)phenyl-2-methyl-4-phenyl-1,2,3,4-
 tetrahydroisoquinoline;
 7- [(4-methyl)-2-thienyl -2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 15 7-[(5-methyl)-2-furanyl]-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 7-(3-furanyl)-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(2-thienyl)-1,2,3,4-tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(3-thienyl)-1,2,3,4-tetrahydroisoquinoline;
 7- [(3,5-dimethyl)-4-isoxazole]-2-methyl-4-phenyl-1,2,3,4-
 20 tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(2-pyridyl)-1,2,3,4-tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(3-pyridyl)-1,2,3,4-tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(4-pyridyl)-1,2,3,4-tetrahydroisoquinoline;
 4-(3,4-difluoro)phenyl-2-methyl-7-(3-pyridyl)-1,2,3,4- tetrahydroisoquinoline;
 25 7-[(2-methoxy)-3-pyridyl]-2-methyl-4-phenyl-1,2,3,4- tetrahydroisoquinoline;
 7-[(6-methoxy)-3-pyridyl]-2-methyl-4-phenyl-1,2,3,4- tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(3,5-pyrimidyl)-1,2,3,4-tetrahydroisoquinoline;
 4-(3,4-difluoro)phenyl-2-methyl-7-(3,5-pyrimidyl)-1,2,3,4-
 tetrahydroisoquinoline;
 30 4-(4-methyl)phenyl-2-methyl-7-(3,5-pyrimidyl)-1,2,3,4- tetrahydroisoquinoline;
 2-methyl-4-phenyl-7-(2,6-pyrimidyl)-1,2,3,4-tetrahydroisoquinoline;
 7-(2,5-dimethyl-4-isoxazole)-4-(4-methoxy)phenyl-2-methyl-1,2,3,4-
 tetrahydroisoquinoline; and

4-(4-methoxy)phenyl-2-methyl-7-(2-pyridyl)-1,2,3,4-tetrahydroisoquinoline or an oxide thereof, a pharmaceutically acceptable salt thereof, a solvate thereof, or a prodrug thereof

5 24. A method according to claim 24, wherein the compound is the (+) stereoisomer.

25. A method according to claim 24, wherein the compound is the (-) stereoisomer.

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